REMARKS

Claims 38 and 39 are rejected under 35 USC 101 because the claimed invention is not supported by either a specific, substantial or credible asserted utility or a well-established utility. The Examiner states that both claims read on polynucleotides that exist in situ and are therefore non-patentable materials. These claims have been canceled. Furthermore, new claims 45-73 include language to clarify that the polynucleotides of the present invention are "purified" and/or "isolated."

New claims 45-73 are further clarified by "degenerate codon equivalents" language. The degeneracy of the genetic code is a concept that is well-known to those skilled in the art and is even discussed in section 2144.09 of the February 2000 revision of the Manual for Patent Examining Procedure as "the fact that most amino acids are specified by more than one nucleotide sequence or codon." Applicant respectfully submits that the new claims are in a condition for allowance and requests that this rejection be withdrawn.

Claims 10, 11, 15, 25, 33, 38 and 39 are rejected under 35 USC 112, second paragraph. The Examiner states that without reference to the specific algorithm used to calculate the percent identity, the metes and bounds of the claims cannot be determined. Although these claims have been canceled, some of the new claims also recite "identity". Thus, Applicant respectfully clarifies the calculation of percent identity in the instant application at this time.

Applicant directs the Examiner's attention to page 11, lines 25-30 of the specification of the instant application, where one embodiment of the software used to calculate percent identity is described. Applicant also respectfully submits the software manual for the Wisconsin Sequence Analysis program, Version 8, publicly available from Genetics Computer Group, Madison WI, as Exhibit A. Support for this submission is found on page 11, beginning on line 25 of the specification. The manual provides the algorithms, parameters, parameter values and other information necessary to calculate percent identity in an accurate and consistent manner. This manual indicates on pages 5-

21, *inter alia*, that the software used the local homology algorithm of Smith and Waterman (Advances in Applied Mathematics 2, pp. 482-489 (1981)). Applicant respectfully submits that the new claims are in a condition for allowance and requests that this rejection be withdrawn.

Claims 10-16, 25, 30, 33, 35 and 38-39 are rejected under 35 USC 112, second paragraph, because they do not conform to the Sequence Rules. Applicant apologizes. These claims have been canceled and the new claims conform to the Sequence Rules. Applicant respectfully submits that the new claims are in a condition for allowance and requests that this rejection be withdrawn.

Claims 10-16, 25, 30, 33, 35 and 38-39 are rejected under 35 USC 112, first paragraph. The Examiner states that the claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

The Examiner states that, based on FIG. 3, two out of six samples of RNA from normal prostate hybridized with the labeled PS116 probe and all five samples of RNA from prostate cancer tissue failed to hybridize with the PS116 probe. The Examiner states that this data is not enabling for the use of these sequences in the detection of prostate cancer. Applicant vigorously disagrees that this is so.

However, in an effort to clarify, Applicant reminds the Examiner a marker protein or marker nucleic acid may not even be present in high levels or at all in every tumor. For example, in the case of the well-known marker HER2-neu, only 1/3 of breast cancers overexpress this protein. Thus, in a breast cancer library, a very low level of HER2-neu will be present even though it is a very accurate breast cancer marker. In fact, HER2-neu is now used as a standard breast cancer marker.

Detection of a particular marker in a cancer patient has profound importance. For instance., for breast cancer patients with overexpression of HER-2-neu, treatment with Herceptin, a human-mouse chimeric antibody directed against the protein has therapeutic value. Also, if the gene which codes for HER-2-neu is amplified (multiple copies are present) as detected by the well known techniques of *in situ* hybridization, again the

patient will likely respond to Herceptin treatment. However, if the patient does not exhibit this amplified gene or overexpression of this protein, treatment with Herceptin is unlikely to be of benefit.

Similarly, testing for estrogen receptor protein by immunohistochemistry in breast cancer patients, indicates treatment with anti-estrogens such as Tamoxifen will have therapeutic value. However, only 2/3 of breast cancer patients actually express estrogen receptor in their tumors and thus benefit from Tamoxifen therapy. Thus, it is clear that the presence or absence of a particular gene product has diagnostic and therapeutic significance for cancer patients.

Furthermore, Applicant respectfully directs the Examiner to Exhibit B, an article entitled "Prostate stem cell antigen: A cell surface marker overexpressed in prostate cancer". This article describes a prostate cancer marker, prostate-specific antigen (PSA), which appears normally in the prostrate and seminal plasma. However, the detection of PSA in blood is indicative of prostate cancer. Further, the appearance of PSA messenger RNA (mRNA) in blood is indicative of prostate cancer. Likewise, the appearance of carcinoembryonic antigen (CEA) in the colon and in stool is normal (i.e. CEA appears normally in its colon host tissue and in stool). However, the appearance of CEA in blood at elevated levels is indicative of colorectal cancer. Similarly, the appearance of PS116 protein or mRNA at elevated levels in a patient blood sample is indicative of prostate disease.

Additionally, it has been found that PS116 is identical to PSCA (prostate stem cell antigen), which has been strongly linked to prostate cancer (see attached Exhibit B). The closest known relative to PS116 besides the identical PSCA is SCA2, normally found in *Gallus gallus* (chicken). The strong homology (i.e., resemblance with conserved cysteine's for disulfide bond conservation) between SCA2 and PS116 is remarkable given the species' difference. SCA2 is a cell surface marker which, like PSCA, is cancer-related. Applicant respectfully directs the Examiner's attention to the attached article Exhibit C, by Oleksi Petrenko, Oncogene (1997) 15, pp 1671- 1680, "Characterization of changes in gene expression associated with malignant transformation by NF-kb family member, v-

Rel", which describes a model for malignant transformation in which SCA2 is shown to be up-regulated when a normal cell is transformed to a malignant cell.

Not only is the homology of PS116 with PSCA and SCA2 indicative of PS116's utility as a cancer marker, but it is also linked to the cell membrane via a glycosylphosphatidylinositol (GPI) anchor, the same type of anchor as PSCA and SCA2. One of the classic tumor markers, CEA, is also GPI-linked to the membranes of cells that express it. This evidence, i.e., the strong homology with known cancer markers and GPI linkages, coupled with PS116's specificity to prostate tissue further illustrates PS116's utility as a prostate tumor marker. In view of the above remarks, Applicant respectfully submits that the new claims are in a condition for allowance and requests that this rejection be withdrawn.

Claims 10-16, 25, 30, 33, 35 and 38-39 are rejected under 35 USC 112, first paragraph. The Examiner states that there is no evidence that at the time of filing, Applicant was in possession of a representative sampling of fragments that are at least 70% identical to fragments of SEQ ID NOS: 1-12 and SEQ ID NOS: 25-29. These claims have been canceled.

However, as stated above, some of new claims 45-73 recite "identity" language. Applicant agrees with Examiner's "broadest reasonable interpretation" that the claims are intended to encompass a variety of species including full-length cDNAs, genes and protein coding regions". Applicant also agrees with the Examiner that the prediction of protein structure from sequence data is extremely complex because of the possibility of variant polypeptides. Applicant asserts that identity language is one means of clearly expressing such a variety of species that may be reasonably discerned from the specification and/or sequence data in the specification by persons skilled in the art. Nevertheless, in an effort to expedite prosecution, Applicant respectfully submits new claims 45-73, which raise the percent identity to 95% and include language to clarify that identity is "over the entire length" of the claimed SEQ ID NO. Fragment language has also been omitted. Applicant respectfully submits that the new claims are in a condition for allowance and requests that this rejection be withdrawn.

The Examiner states that the specification does not list or give examples of amino acid residues which would constitute an epitope or epitopes of SEQ ID NO: 25-29 as claimed in claims 14, 25 and 30. These claims have been canceled. Furthermore, Applicant respectfully traverses the Examiner's statement. The Examiner notes herself that epitope has been clearly defined in the specification and any new claims with "epitope" language are clearly drawn.

The Examiner states that "it would be difficult to predict what peptides an 'epitope' would consist of having only the amino acid sequence of the polypeptides SEQ ID NO: 25-29. Applicant respectfully disagrees. The methods for identifying epitopes in a novel peptide sequence are well known and described in both the scientific, commercial, and patent literature. For example, M. H. Van Regenmortel describes how to predict epitopes from the primary sequence of a protein. (See "Protein structure and antigenicity", *Int J Rad Appl Instrum B.*, **14(4):**277-80, 1987, attached as Exhibit D)

Further, Perkin-Elmer Biosystems, a major provider of DNA sequencing and peptide synthesizing instruments has established a public website which describes how to select peptides which reflect the epitopes of a protein. (See http://www.pebio.com/pa/340913/html/chapt2.html#Choosing the Epitope.) This electronic publication has been posted since 1996 and basically describes the process employed by the inventors of the current patent application.

In addition, patent application PCT/US97/00485 describes in detail how to identify epitopes from peptide sequences. The sequence can be scanned for hydrophobicity and hydrophilicity values by the method of Hopp, Prog. Clin. Biol. Res. 172B: 367-377 (1985) (Exhibit E) or the method of Cease et al, J. Exp. Med. 164: 1779-1784 (1986) (Exhibit F) or the method of Spouge et al, J. Immunol. 138: 204-212 (1987)(Exhibit G). Commercial software programs to implement these methods are also available. Thus, it is respectfully requested that this rejection be withdrawn.

Claims 10-16, 25, 30, 33, 35, 38, and 39 are rejected under 35 USC 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had

possession of the claimed invention. In view of the above remarks, Applicant respectfully submits that the new claims are in a condition for allowance and requests that this rejection be withdrawn.

CONCLUSION

In view of the aforementioned amendments and remarks, Applicant respectfully submits that the above-referenced application is now in a condition for allowance and Applicant respectfully requests that the Examiner withdraw all outstanding objections and rejections and passes the application to allowance.

Respectfully submitted,
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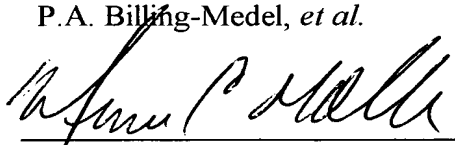

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